Journal of Forensic and Legal Medicine 18 (2011) 66–72

Contents lists available at ScienceDirect

Journal of Forensic and Legal Medicine

journal homepage: www.elsevier.com/locate/jflm

Original Communication

Causes of premature mortality in Swedish drug abusers: A prospective longitudinal study 1970–2006

Anna Nyhlén MD, PhD Senior Consultant (in Psychiatry) [a,b,*], Mats Fridell PhD Professor [c,d], Morten Hesse PhD Assist. Professor [e], Peter Krantz MD, PhD Assoc. Professor [f]

[a] Department of Infectious Diseases, Lund University Hospital, Kioskgatan 19, 221 85 Lund, Sweden
[b] Department of Psychiatry, Lund University Hospital, SE - 221 85 Lund, Sweden
[c] Department of Psychology, Lund University, Sweden
[d] Vaxjo University, School of Education, Psychology and Sport Science, B 213, SE-351 95 Växjö, Sweden
[e] University of Aarhus, Centre for Alcohol and Drug Research, Artillerivej 90, 2300 København S, Denmark
[f] Department of Forensic Medicine, Lund University Hospital, S - 221 85 Lund, Sweden

ARTICLE INFO

Article history:
Received 2 August 2010
Received in revised form
8 December 2010
Accepted 5 January 2011
Available online 1 February 2011

Keywords:
Cohort study
Long-term follow-up
Drug-related deaths
Gender
Forensic autopsy
Suicide
ICD-10

ABSTRACT

Aims: To evaluate premature mortality and causes of death from young adulthood to middle age in a cohort of drug users followed during almost four decades
Design: Follow-up study of a consecutive cohort of patients with drug abuse/dependence.
Methods: A cohort of 561 drug abusers, admitted to a detoxification and short-term rehabilitation unit 1970–1978 was followed to December 31st, 2006. Standardized interviews and hospital records with toxicological analyses were used for demographic data, substance use and psychiatric diagnoses at admission. For Follow-up analyses, autopsy protocols including toxicology tests and death certificates were obtained for assessment of causes of death which were coded according to ICD-10. Age-group standardized mortality ratios were calculated independently for both sexes.
Results: 204 persons (36.4%) were deceased by 2006. SMR was 5.94 for the cohort. Compared to an age- and gender-matched population, the risk of premature death was about eighteen times higher between the ages of 20–44 and about five times higher from 45 up to the age of 69. Of 120 (59%) drug-related deaths, 43 were opiate overdoses, and 3 were overdose from amphetamine. A total of 53 (26%) persons died violent deaths: 39 suicides, of which 25 were drug-related, 3 homicides and 12 accidents. The Swedish national causes of death register underestimated drug-related death by 37% and suicide by 85% compared to the results from this study.
Conclusions: The cohort of drug abusers had an increased risk of premature often drug-related and violent death well into middle age, and to a great extent the drug addicts died from the same drug they had abused when they were first admitted for treatment. The underestimation of drug-related death and suicide in some national death cause registers could be reduced if the doctor routinely records ICD codes when issuing death certificates and autopsy protocols.

1. Introduction

Drug abusers have an increased risk of premature mortality, which is influenced by a number of factors, including types of drugs used, patterns of administration, risk behavior, contracted infectious diseases, gender, age and social situation. Premature death is defined as death occurring before the average age of death within a given population.

The present study investigates causes of premature death in a cohort of drug abusers from January 1970 to December 31st, 2006. During the 1970s drug use patterns in Sweden changed from a predominance of amphetamine abuse to amphetamine as well as opiate abuse.[1,2] Regional differences in the availability of substances have remained to the present.[3] In Copenhagen in Denmark, very close to the studied county in the southern part of Sweden, morphine base and, from 1975, heroin, have dominated the drug scene.[4] The cohort is, according to data from a national case-finding study from the 1970s, representative of the pattern of heavy drug use in the population of substance abusers at that time. Most of the local intravenous drug abusers were included in this cohort as patients.[3]

* Corresponding author. Department of Infectious Diseases, Lund University Hospital, Kioskgatan 19, 221 85 Lund, Sweden. Tel.: +46 46 174995; fax: +46 46 174990.
E-mail address: anna.nyhlen@skane.se (A. Nyhlén).

1752-928X/$ – see front matter
doi:10.1016/j.jflm.2011.01.003

Modes of administration vary between drug-dependent populations. Intravenous drug use in particular is vital to evaluate, since some contagious blood-borne infections cause chronic infections and even death. Contagious blood-borne infections related to intravenous drug use are hepatitis B, hepatitis C and HIV.[5–10] In USA, the first HIV infections appeared among drug addicts in New York in the mid 1970s,[11] while in Sweden the first HIV-infected drug addict was detected as late as 1984.[12]

Most studies report higher mortality for opiate users than for other substance users[13–17] but most substance dependent patients use more than one substance throughout life. A follow-up study of a consecutive sample of 125 drug-dependent Swedish patients with mixed drug abuse demonstrated an annual mortality rate of 1%,[18] a figure which increased to 2% over the next ten year follow-up period of the same sample.[19]

1.1. The drug scene

Around 16.5 million persons use opiates per year worldwide.[20] In a meta-analysis of mortality death rates among opiate abusers were about 13 times the norm for their age.[21] The standardized mortality ratio (SMR) in more recent studies is still higher in groups that do not receive opiate agonist treatment such as methadone, buprenorphine or other opiates.[7,17,22–25] In general, mortality is suppressed during opiate agonist maintenance treatment or heroin maintenance.[25]

Overdose is a major cause of death among opiate-dependent patients. In Australia it is assumed that 1/140 opiate users (0.7%) die from an overdose in a given year.[26] Overdose is here defined as death caused by illicit drugs.[27] Several studies of opiate users have reported that 35–40% of all deaths are overdoses.[6,14,28–31] Lifestyle is a major influence factor. Overdoses, for instance, seldom occur among subjects who have become opiate-dependent in connection with pain treatment[32] or among abusers not injecting.[33]

Although amphetamine is considered to be the most prevalent synthetic drug of abuse in the world used by 25 million individuals per year, few studies have focused on the impact of stimulant use on cause specific mortality.[20,34] Unlike opiates, cocaine and amphetamine seldom cause death.[26] Instead, stimulant use has been associated with increased mortality due to lifestyle factors indirectly associated with stimulant use such as violent behavior, violent deaths or diseases acquired through intravenous administration.[12,35]

Despite the fact that cannabis in its various forms is the most common substance worldwide, used by as many as 166 million people per year, few studies have to our knowledge assessed mortality associated with cannabis or reported an increased association between mortality and cannabis. One study of marijuana smokers reported that cannabis was associated with increased AIDS-related mortality,[36] an association explained by an increased prevalence of marijuana use among homosexual males.

1.2. Influence of psychiatric disorders

The relation between premature mortality and psychiatric disorders in drug abusers has to our knowledge never previously been studied in a cohort over several decades. The suicide rate in epidemiological studies of drug abusers is high and suicide attempts often reflect a co-morbid depressive disorder.[37] The rate of suicide attempts in a five-year follow-up of a representative sample from the present material demonstrated that 45% of all patients had attempted suicide at least once.[18] Another Swedish study observing patients with co-morbid substance abuse and psychiatric disorders found a rate of 59% attempted suicides.[38]

1.3. Aims of the study

I. To compare the mortality in the cohort of drug-dependent patients with the mortality in a gender- and age-corrected local population in the southern region of Sweden.
II. To identify causes of death in the cohort: (1) Drug-related: (a) drug as primary, underlying death cause, including overdosing and drug-related suicides (b) drug as contributing cause of death, including violent death, (2) To identify non drug-related deaths: (a) diseases, (b) violent death including accidental death and suicide/homicide.
III. To identify to what extent substances found post mortem were already present at the first admission to treatment.

2. Method

2.1. Setting

The setting was an inpatient detoxification and short-term rehabilitation unit in the southern part of Sweden, Scania County, at the St. Lars psychiatric hospital in the city of Lund. The catchment area for the unit was the entire county with a population of 977,783 people in 1970. The unit was a typical low threshold treatment facility of this period accepting all drug abusers seeking treatment.

2.2. Subjects

The data were collected over a period of nearly four decades prior to the follow-up conducted in 2006. Comparisons were made between those who were alive in December 2006 and those who had died during the study period 1970–2006. Causes of death were analyzed for all individuals who died during the follow-up.

2.3. Assessment at baseline

Drug use and somatic symptoms were evaluated in the regular medical intake assessment carried out by a physician. Drug screening, including alcohol, was based on intake urine samples analyzed by thin layer chromatography or gas chromatography at the laboratory unit of the hospital. Standardized forms were used for collecting baseline demographic data, types of drugs used and psychiatric disorders. Clinical interviews, standardized questionnaires (SWEDATE) and hospital records contained mandatory information on length, intensity of substance abuse and psychiatric diagnoses.[39,40] Diagnoses of psychiatric disorders were issued at discharge by the senior consulting psychiatrist. For this presentation, three broad groups according to ICD-8 nomenclature were used: psychosis, neurotic disorder (depression and/or anxiety disorders) and personality disorder.

2.4. Coding and identifying causes of death

In this long-term follow-up of mortality, the patients' national identification numbers were linked to the Swedish Central Personal Register and the Cause of Death Register at the National Department of Health (EPC) in which all deaths are consistently recorded by the Swedish Central Bureau of Statistics (SCB). The coding in Sweden is performed by SCB, based upon death certificates, issued but not coded by physicians and/or forensic doctors. The coverage of deaths in Sweden is close to 100% because reporting is mandatory. The ICD-10 codes permit classification of death causes according to the rules specified in the International Statistical Classification of Diseases and Related Health Problems, published by the WHO.[41] ICD-10 provides improved coding possibilities for many different drugs compared to previous versions of ICD.

Diagnoses in hospital records from the first admission based on ICD-8 and ICD-9 (303, 304) were re-coded into ICD-10 diagnoses of substance abuse and dependence (F10–F19).

Death certificates and autopsy protocols from forensic clinics in Sweden and Denmark were obtained, and causes of death were coded according to ICD-10 by a senior consultant physician (A.N.) and an associate professor of forensic medicine (P.K.). Causes of death were finally classified as drug-related or non drug-related. The two raters classified the first 100 causes of death diagnoses independently of each other. All cases ($n = 204$) were then filed after mutual agreement. Only three out of 100 differed slightly (3%). A reliability check of 70 protocols classifying drug-related vs non drug-related deaths showed a good agreement ($\kappa = 0.98$).

Swedish forensic autopsy always includes drug analyses when the deceased persons are drug abusers, and/or persons who have suffered an accidental, unclear or violent death. These toxicological data were studied in detail in every case of suspected or confirmed drug-related death.

Violent death includes accidental deaths and suicides/homicides and can be both drug-related and non drug-related. Accidental death includes, for example, motor vehicles and drowning accidents. Overdoses were classified separately by type of drug. Overdose is defined as an acute death, occurring shortly after the intake of an illegal drug, and directly related to the intake of the drug.[27] Overdoses are often presumed to be accidental but can be suicidal with a lethal intoxication with illicit drugs. Suicidal overdoses were classified as suicides by the pathologist on the basis of forensic autopsy protocols. Police reports supplied important additional information to confirm diagnoses.

2.4.1. Drug-related death

2.4.1.1. Drug as underlying cause of death. The underlying cause of death is the primary reason for dying, while contributing causes of death contribute to death without being the primary cause.[27] The definition of drug-related death used is the one adopted by several other authors.[5,27] The outline of classification of drug-related death presented by Degenhardt[26] is close to the one used in this study with additional ICD-10 codes to include alcohol, as well as self-inflicted and unclear intoxication by any drug. Drug-related death, "drug-induced death" refers to those cases where the underlying cause of death is directly associated to drug use according to death certificates or autopsy protocols. The primary cause of drug-related death is defined according to the substances involved and the context.

i) an acute condition caused by drug use where the deceased person was identified as having a drug use disorder (F10–F16, F19), usually with a history of drug dependence (F10.2–F16.2, F19.2) and ii) an acute intoxication, caused by drugs (X40–X45, X60–X65, or/and codes from T36–T50 for specific drug identification, or/and X85 + Y10–Y15).

ii) A primary drug-related death includes the codes F10.0–F16.0, F19.0 alone or X40–X45/X60–X65 cross-classified with alcohol (F10.0), cocaine (T40.5, F14.0), other stimulants as amphetamine (T43.6, F15.0), or opiates (T40.0–T40.4, T40.6 and F11.0).

2.4.1.2. Drug as contributing factor in deaths due to other causes. Cases where drugs play only a contributory role (indirectly related to death, e.g. motor vehicle accidents, drowning) or the underlying cause of death is a medical condition caused by long-term use of drugs, the use of drugs is not classified as primary cause of death.

2.4.2. Non drug-related death

Non drug-related death was classified as such if death was caused by somatic diseases as well as accidents, suicide or other violent deaths without laboratory indications of drug involvement.

3. Statistical analysis

First, the observed mortality rates of the subjects in the sample were compared with the mortality in the general population in the area, Scania County, Sweden in the 1970s, by calculating the SMR for both genders combined in 5-year age groups. The general population mortality was adjusted to match the gender and age distribution of the drug-user population. SMR was calculated as the ratio, observed/expected for men and women separately. Subjects were censored by December 31, 2006.

Within each 5-year age group, the number of subjects at risk was calculated as the number of subjects who 1) entered the cohort before they reached that age-group interval, 2) had not died or migrated before that age-group interval, and 3) had not passed that age-group interval to December 2006. Since the ethnic diversity of Sweden was small in the 1970s, adjusting for race or ethnicity was not considered necessary.

4. Results

4.1. Characteristics of the cohort

The cohort was predominately young males, 23–25 years old at first admission to detoxification (Table 1). A family history of substance use problems was reported for about 40%, and psychiatric illness in the family was present in about 20% of the cohort. More than a third of the patients never completed grammar school and 40% had a history of imprisonment. The incidence in the cohort

Table 1
Descriptive data at baseline 1970–1978 ($n = 561$), percentages.

	Deceased in 2006	Alive in 2006	Total
Demographics (as indicated)			
Age at first detoxification	$m = 25.9$ SD/range 8.8/13–68	$m = 23.2$ SD/range 5.9/13–50	$M = 24.3$ (SD = 7.2)
	%	%	%
Female gender	24	37	32
History of prison	41	35	34
Education			
–Not completed grammar	36	36	37
–Grammar school	52	56	54
–Graduated high school	7	3	4
–University studies	4	4	4
Family background at baseline[a]			
Raised by both parents	55	56	56
Raised by single parent	40	37	38
Substances			
Opiates	40	27	34
Stimulants (mostly Amphetamine)	37	48	42
Barbiturates	18	9	15
Cannabis	47	61	51
Problems in family of origin			
Psychiatric disorder in family	20	16	18
Substance use in family	42	37	39
Hepatitis at baseline			
Hepatitis (A, B, non A–non B)[b]	51	46	48
Psychiatric conditions at baseline			
Psychosis	9	16	14.4
Neurosis	14	15	14.8
Personality disorder	19	21	20.1

[a] Missing data for 10% in both groups.
[b] It was not possible to diagnose hepatitis C before 1991.

was about 50% for hepatitis B at baseline. Testing for hepatitis B commenced about 1975, for HIV in 1988, and for hepatitis C in 1999.

The substances most frequently used at first admission were opiates (35%), stimulants (36%), cannabis (45%) and barbiturates (13%). A majority of the patients had an intense substance use lasting for more than one year corresponding to a diagnosis of substance dependence. Regular intravenous drug use was reported by around 80% of the patients in the cohort. Almost all opiate users and amphetamine users were intravenous users. There were no gender differences in substance use and only opiates ($p < 0.02$) and cannabis ($p < 0.009$) were significantly more common among males. Deceased patients used more opiates and barbiturates than those alive in 2006.

About 50% of the individuals suffered from at least one psychiatric disorder (Table 1). Psychiatric disorders categorized into psychosis, neurotic disorder and personality disorder had no significant influence on premature mortality when comparing deceased vs alive ($\chi^2 = 1.86$, n.s.). Of the suicide cases, 32% were diagnosed with psychosis at baseline.

A national case-finding study estimated that the number of heavy drug abusers in the Southern region, having a daily intake of illegal drugs was around 1300 in 1978, 50% being injection drug users.[3] The proportions of males, age and dominating drug pattern in the cohort were reasonably similar to those in the case-finding study. A majority of the intravenous abusers in the region were patients in the cohort, excluding persons below the age of 17. The intravenous drug abusers in the cohort can be regarded as representative of intravenous abusers in the local population of substance abusers.

4.2. Mortality rates

By the end of 2006, 204 of 561 patients in the cohort (36.4%) had died. Two percent had either immigrated or could not be located. The standard mortality ratio (SMR) in the entire sample is summarized in Table 2. The crude annual mortality was 1.3%, the expected number of deaths was 34.4 and the SMR was 5.94 (95% CI = 5.5–6.81), compared to the local gender- and age-matched population.

Premature mortality in the cohort was highest among the patients in their early twenties, and remained at a high level well into middle age. As is evident from Table 2, the crude annual mortality in the group remained stable until middle age.

The gender-specific mortality is shown in Table 3. For men, the observed number of deaths was 158 based on 10,420 observation years, while the expected number of deaths was 28.3. SMR was 5.6 (95% CI = 4.8–6.5), and the crude mortality ratio was 1.5%. For women the observed number of deaths was 46 based on 5265 observation years, while the expected number of deaths was 11.

SMR was 4.2 (95% CI = 2.99–5.41), and the crude annual mortality was 0.9%. The difference between the genders was not significant, but for certain age groups SMR varied considerably.

Table 2
Standardized mortality ratio by age groups.

Age span	*N* of person-years at risk	*N* dying	Crude annual mortality	Expected mortality[a]	Standard mortality ratio	95% Confidence intervals	
						Lower	Higher
15–19	395.56	1	0.30%	0.05%	8.33	0.21	46.43
20–24	1674.58	25	1.50%	0.07%	29.07	18.81	42.91
20–29	2220.31	23	1.00%	0.07%	15.64	9.92	23.48
30–34	2274.44	30	1.30%	0.09%	17.75	11.98	25.34
35–39	2214.02	24	1.10%	0.12%	15.00	9.61	22.31
40–44	2145.03	30	1.40%	0.19%	10.91	7.36	15.57
45–49	2037.31	28	1.40%	0.28%	6.93	4.61	10.02
50–54	1659.27	24	1.40%	0.46%	4.33	2.78	6.46
55–59	764.19	9	1.20%	0.76%	2.24	1.03	4.26
60–64	219.10	6	2.70%	1.23%	3.43	1.26	7.46
65–69	82.32	4	4.90%	2.03%	3.88	1.06	9.94

Expected mortality rate is weighted to match the gender composition of the cohort.
[a] Based on the average of the years 1970–1995 in the local area (the region of Scania, Sweden).

Table 3
Standardized mortality ratio by gender.

	N of person-years at risk	*N* dead	Crude annual mortality	Expected mortality[a]	Standard mortality ratio	Lower	Higher
Men							
15–19	236.7	1	0.4%	0.06%	10.41	0.26	58.03
20–24	1093.72	18	1.6%	0.09%	22.80	13.50	36.01
20–29	1497.48	19	1.3%	0.09%	14.72	8.87	23.00
30–34	1543.53	24	1.6%	0.10%	16.21	10.39	24.13
35–39	1497.18	20	1.3%	0.14%	16.52	10.10	25.52
40–44	1421.40	22	1.5%	0.22%	10.23	6.41	15.50
45–49	1332.86	23	1.7%	0.33%	8.33	5.28	12.50
50–54	1091.90	20	1.8%	0.54%	5.13	3.13	7.92
55–59	523.04	6	1.1%	0.90%	1.90	0.70	4.15
60–64	142.10	3	2.1%	1.48%	2.42	0.50	7.07
65–69	40.81	2	4.9%	2.45%	3.13	0.38	11.29
Women							
15–19	158.86	0	0.0%	0.02%	NE		
20–24	580.86	7	1.2%	0.03%	32.26	11.83	70.21
20–29	722.83	4	0.6%	0.04%	22.47	6.12	57.53
30–34	730.91	6	0.8%	0.05%	28.57	10.48	62.18
35–39	716.84	4	0.6%	0.08%	10.26	2.79	26.26
40–44	723.63	8	1.1%	0.12%	13.36	5.77	26.33
45–49	704.45	5	0.7%	0.20%	3.90	1.27	9.10
50–54	567.37	4	0.7%	0.31%	2.45	0.67	6.28
55–59	241.15	3	1.2%	0.47%	3.49	0.72	10.19
60–65	77.09	3	3.9%	0.73%	5.82	1.20	17.01
66–70	41.51	2	4.8%	1.19%	5.05	0.61	18.24

[a] Based on the average of the years 1970–1995 in the local area (the region of Scania, Sweden).

4.3. Causes of death

The causes of death were coded by ICD-10 diagnoses for all deceased persons in the cohort ($n = 204$). The coding was based on death certificates and autopsy reports from departments of Forensic Medicine (85%) or, to a minor extent, on autopsy reports from general hospitals (5%). Medical records and police reports provided additional information. Causes of death were divided into drug-related or non drug-related death, and sub-grouped according to the labels in Fig. 1.

4.3.1. Drug-related death

Drug-related death was the primary cause of death in 120 cases (59%). Toxicological analyses were provided for all these cases.

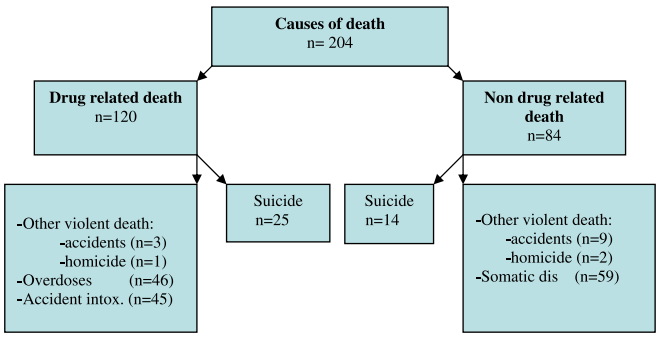

Fig. 1. Drug-related and non drug-related causes of death in the cohort.

Autopsy protocols with toxicological analyses provided data which would otherwise have been obscured. In this group 46 deaths were caused by overdoses of illegal drugs, of which 43 (93%) involved opiates and 3 (7%) stimulants (amphetamine mostly). Seventy of the remaining 74 deaths were intoxications by one or several legal drugs, sometimes in combination with illegal drugs. Mixed intoxication was diagnosed in 54% of all the cases of fatal intoxication. Drug-related death due to suicide was diagnosed in 25/120 deaths (21%). In all, 25% died a violent drug-related death from suicide, homicide or accidents.

The group with primary alcohol dependence was only 3%, but still was overrepresented in violent death ($p = 0.002$). Drug-related death was underestimated by 37% (76 vs 120 cases) and suicide by 85%, (6 vs 39 suicides) when comparing the ICD-codes from the study with the codes from the Swedish national death cause register. In the first case drug diagnoses were missing and in the second, X-codes for self-inflicted causes of death were missing in the death certificates from SCB.

Post mortem drug analyses were compared to drug dependence diagnoses at baseline (Table 4).

One third of the cohort had an opiate dependence at baseline and 40% (70/174) of them were dead by the end of 2006. Of the opiate abusers, 43 died from opiate overdoses and the remaining died from mixed intoxications with opiates. Sedative and hypnotic drugs exclusively were found post mortem in 56 persons of which 16 was barbiturate intoxications. Of these deaths 10/16 barbiturate intoxications were mixed with other drugs, mostly alcohol and opiates. Alcohol was present post mortem in 23%, mostly detected in combination with other drugs.

4.3.2. Non drug-related death

Somatic diseases were the primary cause of death in 29% of all deaths of the cohort. Somatic death causes were cardiovascular diseases ($n = 24$), liver cancer ($n = 5$), and other forms of cancer ($n = 8$). Three died from terminal AIDS. The remaining 19 individuals died mainly from other infections such as pneumonia, hepatitis and septicemia. The time from first treatment contact to death was longer for subjects who died from somatic diseases than for those who died from accidental intoxication or violent death as suicide, homicide, accidents. Non drug-related death was violent in 30% of the cases, caused by suicide, by homicide or by accidents (Fig. 1).

Table 4
Substances and combinations of substances detected at post mortem examination, and the frequency of substance dependence in the same group of individuals at baseline ($n = 204$).

Substance	Post mortem	Percentage of all deaths	Baseline dependence diagnosis
Opiates	70	34	43
Sedatives and hypnotics[a]	56	27	6
Alcohol	46	23	21
Barbiturates	16	8	27[b]
Central stimulants (CS)	14	7	8
Cannabis	2	1	2
Other drugs[c]	12	6	No data
Mix of substances in addition to the primary substance listed above[d]			
Opiates + sedatives/hypnotics	27	13	5
Sedatives/hypnotics + alcohol	23	11	No data
Opiates + alcohol	20	10	15
CS, alcohol + other	14	7	3
CS, opiates + sedatives/hypnotics	11	5	9

For this reason percentages do not total 100%.
[a] Bensodiazepines were detected in 28/204 (13%).
[b] Barbiturates were withdrawn from the legal market in Sweden in 1985.
[c] Paracetamol, dextropropoxiphen, tramadolhydrochlorid, antidepressants, fentiazines.
[d] Frequencies and percentages are provided for every observation of drugs alone or in combinations.

5. Discussion

This prospective study of substance abusers followed over four decades confirms the long-lasting increased risk for premature death from drug addiction. In the years from age 20 to the mid-thirties, drug users in the cohort showed a ten-fold or higher risk of dying compared to the general population in the area. An earlier studied smaller cohort of mostly heroin abusers had a crude annual mortality rate of 2.5%.[16] The present cohort with a mixed group of substance abusers had a mean crude annual mortality rate of 1.31%. Premature mortality of the drug abusers remained significantly increased up to the age of 65. These findings are consistent with a Danish cohort study of opiate addicts still being at higher risk of premature death after many years of stable abstinence.[24]

Around 60% of the cohort individuals in the present study used more than one drug at baseline, and many remained mixed abusers throughout life. One third of the opiate-related deaths in the present study were mixed intoxications with alcohol and sedatives. When analyzing causes of death by specific drug intoxications as well as intoxications by combinations of drugs, we found a pattern of post mortem substances very similar to a study by Gossop et al.[29]: opiates was the most prevalent group of substances found at death, followed by all types of sedative and hypnotic drugs, such as barbiturates, benzodiazepines, and alcohol. Substances found post mortem reflected fairly stable patterns of drug use over time. About 50% of the patients died from the same substance they abused already at first admission.

Two earlier Swedish studies[2,16] showed that regular opiate use was related to premature mortality and male gender. The generally lower level of premature mortality in women as previously reported in other studies of Scandinavian drug abusers[13,16,44] was not confirmed. Rather, the SMRs for women were higher in certain young age groups compared to SMRs in men. Thus the mixed picture of elevated premature mortality rates for male drug users in some studies,[14,33] lower rates of male premature mortality[32] in others, or no gender differences[5,19,28,45] might reflect specific subgroup patterns rather than general gender differences.

In this cohort 45 of 70 opiate-related deaths were overdoses. Overdose is the major cause of death among opiate-dependent patients, and accounts for 35–40% of deaths,[28] sometimes at dosage levels that are not higher than their regular doses.[42] One reason is that non lethal doses of heroin can become lethal in the presence of alcohol and sedatives such as benzodiazepines.[42] Barbiturates mixed with opiates have an additive depressive effect on respiration.

In a study from Australia,[14] the risk of drug-related death for opiate addicts was 2.4 times higher than for amphetamine users. The mortality rate related to stimulants was low, consistent with earlier findings.[26] Only 3 of 46 overdoses were due to amphetamine in our study while 11/70 fatal intoxications involved amphetamine as one of several mixed substances.

The association between cannabis use and mortality was negative in the earlier study from the same cohort.[16] This finding remains in the present larger cohort also after controlling for the use of other drugs. Cannabis was rarely found post mortem despite the fact that half of the patients were introduced to the drug scene with cannabis and 15% of the cohort used cannabis at the first admission. Our conclusions are consistent with other studies stating that cannabis is not associated with increased premature mortality.[36,46]

Premature death was elevated in patients in this cohort who were abstinent from heavy drug abuse when followed-up after fifteen years, but 10–15% lower compared to those in active drug

use.[19] These findings are consistent with other long-term cohort studies.[31,47] Although mortality decreases with continued abstinence it remains higher than in the general population[15,24]

Although the incidence of psychiatric disorders in the cohort was around 50% and some researchers have suggested a causative impact of psychopathology on premature mortality[14,43,44] this immediate association was not confirmed in this study. This is in agreement with Sørensen, Jepsen, Haastrup et al.[24] Nevertheless a substantial finding was that 32% of the suicide cases in the cohort had been diagnosed with psychosis at baseline. The proportion of suicide in this cohort was about 10 times higher than in the general population in Sweden.[8]

Another third of the deceased died from somatic diseases associated with drug addiction, mostly liver failure, liver cancer and infections such as pneumonia and blood-borne infections: HIV, hepatitis B/C, and septicemia. The low incidence of HIV/AIDS reflects the low prevalence of HIV in Sweden.

Among the assets of this study are the long observation period and the completeness of individual data, which allowed us to describe the cohort in detail from their first admission and follow the patients over time with data seldom available when register data are the only available tool. The characteristics of the cohort also showed a fair agreement with corresponding characteristics in the population of heavy drug abusers in Southern Sweden as assessed in repeated case-finding studies.[3]

Finally, the procedure where two medical experts coded death causes, eliminated some inconsistencies found in data from national registers. In line with Gossop's observation, the use of autopsy protocols identified a larger and more correct proportion of drug-related deaths than did register data alone.[29] This validity problem could be reduced if the same medical doctor issuing the death certificates and the autopsy protocols also make the final coding using modern ICD-10 standard.

A drawback is that the cohort design by necessity provides a more limited number of subjects for analysis, thus restricting power more than is the case in large epidemiological samples.

5.1. Conclusions

When drug abuse is serious enough to warrant detoxification, it is associated with premature mortality well into middle age. The drugs found post mortem were to a high degree the same drugs abused at baseline, implicating that many of the drug addicts had a consistent heavy substance abuse of the same drugs throughout life. The underestimation of drug-related death and suicide in some national causes of death registers could be reduced if the same doctor issue and code ICD-diagnoses on the death certificates and autopsy protocols.

Conflict of interest

There are no conflicting interests. Nor are there any conflicting interests between authors of the article or in relation to the departments to which the authors are affiliated.

Funding

The study is financed by external non-profit organizations and the study results are not of commercial interest, only scientific.

Ethical approval

The study was approved by the Ethical Committee of Lund University (LU 22/1983 and Dnr 587/2005).

Acknowledgments

This research was supported by the Commission for Social Research, Stockholm (Grant # SFR 92-0244:1b), The Mobilization Against Drugs, Stockholm (Grant # MOB-DNR 238/2006:39), and the Swedish Prison and Probation Service (Grant # Dnr. 52-2007-28104). The study was approved by the Ethical Committee of Lund University (LU 22/1983 and Dnr 587/2005).

References

1. Bejerot N. Drug abuse and drug policy. An epidemiological and methodological study of drug abuse of intravenous type in the Stockholm police arrest population 1965–1970 in relation to changes in drug policy. *Acta Psychiatr Scand* 1975;**256**(Suppl.):3–277.
2. Frykholm B. Changes in short-term prognosis – a comparison between Swedish amphetamine and opiate abusers. *Drug Alcohol Depend* 1980 Feb;**5**(2):123–8.
3. UNO. *Heavy drug use. A special report for counties and municipalities of the 1979 study*. Stockholm: Liber; 1980.
4. Young Haastrup S. *Drug abusers – 350 patients interviewed at admission and followed up three years later*. Copenhagen: Munksgaard; 1973.
5. Bargagli AM, Sperati A, Davoli M, Forastiere F, Perucci CA. Mortality among problem drug users in Rome: an 18-year follow-up study, 1980–97. *Addiction* 2001 Oct;**96**(10):1455–63.
6. Brugal MT, Domingo-Salvany A, Puig R, Barrio G, Garcia de Olalla P, de la Fuente L. Evaluating the impact of methadone maintenance programmes on mortality due to overdose and aids in a cohort of heroin users in Spain. *Addiction* 2005 Jul;**100**(7):981–9.
7. Copeland L, Budd J, Robertson JR, Elton RA. Changing patterns in causes of death in a cohort of injecting drug users, 1980–2001. *Arch Intern Med* 2004 Jun 14;**164**(11):1214–20.
8. Kohli R, Lo Y, Howard AA, Buono D, Floris-Moore M, Klein RS, et al. Mortality in an urban cohort of HIV-infected and at-risk drug users in the era of highly active antiretroviral therapy. *Clin Infect Dis* 2005 Sep 15;**41**(6):864–72.
9. Johnson JE, Finney JW, Moos RH. Predictors of 5-year mortality following inpatient/residential group treatment for substance use disorders. *Addict Behav* 2005 Aug;**30**(7):1300–16.
10. van Ameijden EJ, Langendam MW, Coutinho RA. Dose–effect relationship between overdose mortality and prescribed methadone dosage in low-threshold maintenance programs. *Addict Behav* 1999 Jul–Aug;**24**(4):559–63.
11. Des Jarlais DC, Friedman SR, Novick DM, Sotheran JL, Thomas P, Yancovitz SR, et al. HIV-1 infection among intravenous drug users in Manhattan, New York City, from 1977 through 1987. *J Am Med Assoc* 1989 Feb 17;**261**(7):1008–12.
12. Fugelstad A. *Drug-related Deaths in Stockholm During the period 1985–1994. Causes and manners of death in relation to type of drug abuse, HIV-infection and methadone treatment*. Stockholm: Karolinska Institute; 1997.
13. Wahren CA, Brandt L, Allebeck P. Has mortality in drug addicts increased? A comparison of two hospitalized cohorts in Stockholm. *Int J Epidemiol* 1997;**26**(6):1219–26.
14. Bartu A, Freeman NC, Gawthorne GS, Codde JP, Holman CD. Mortality in a cohort of opiate and amphetamine users in Perth, Western Australia. *Addiction* 2004 Jan;**99**(1):53–60.
15. Barr HL, Antes D, Ottenberg DJ, Rosen A. Mortality of treated alcoholics and drug addicts: the benefits of abstinence. *J Stud Alcohol* 1984 Sep;**45**(5):440–52.
16. Tunving K. Fatal outcome in drug addiction. *Acta Psychiatr Scand* 1988;**77**(5):551–66.
17. Skurtveit S, Christophersen AS, Grung M, Morland J. Increased mortality among previously apprehended drunken and drugged drivers. *Drug Alcohol Depend* 2002 Oct 1;**68**(2):143–50.
18. Johnsson E, Fridell M. Suicide attempts in a cohort of drug abusers: a 5-year follow-up study. *Acta Psychiatr Scand* 1997 Nov;**96**(5):362–6.
19. Fridell M, Hesse M. Psychiatric severity and mortality in substance abusers: a 15-year follow-up of drug users. *Addict Behav* 2006 Apr;**31**(4):559–65.
20. UNODC. *World drug report*. New York: United Nations Office of Drugs and Crime; 2008.
21. Hulse GK, English DR, Milne E, Holman CD. The quantification of mortality resulting from the regular use of illicit opiates. *Addiction* 1999;**94**(2):221–9.
22. Risser D, Honigschnabl S, Stichenwirth M, Pfudl S, Sebald D, Kaff A, et al. Mortality of opiate users in Vienna, Austria. *Drug Alcohol Depend* 2001 Nov 1;**64**(3):251–6.
23. Rehm J, Frick U, Hartwig C, Gutzwiller F, Gschwend P, Uchtenhagen A. Mortality in heroin-assisted treatment in Switzerland 1994–2000. *Drug Alcohol Depend* 2005 Aug 1;**79**(2):137–43.
24. Sørensen HJ, Jepsen PW, Haastrup S, Juel K. Drug-use pattern, comorbid psychosis and mortality in people with a history of opioid addiction. *Acta Psychiatr Scand* 2005;**111**:244–9.
25. Degenhardt LJ, Randall D, Hall W, Law M, Butler T, Burns L. Mortality among clients of a state-wide opioid pharmacotherapy program over 20 years: risk factors and lives saved. *Drug Alcohol Depend* 2009;**105**:9–15.
26. Degenhardt LJ, Roxburgh A, Barker B. Underlying causes of cocaine, amphetamine and opioid related deaths in Australia. *J Clin Forensic Med* 2005;**12**(4):187–95.
27. Buster CA, van Brussel GHA, van den Brink W. An increase in overdose mortality during the first 2 weeks after entering or re-entering methadone treatment in Amsterdam. *Addiction* 2002;**97**:993–1001.

28. Oppenheimer E, Tobutt C, Taylor C, Andrew T. Death and survival in a cohort of heroin addicts from London clinics: a 22-year follow-up study. *Addiction* 1994 Oct;**89**(10):1299–308.
29. Gossop M, Stewart D, Treacy S, Marsden J. A prospective study of mortality among drug misusers during a 4-year period after seeking treatment. *Addiction* 2002 Jan;**97**(1):39–47.
30. Frischer M, Bloor M, Goldberg D, Clark J, Green S, McKeganey N. Mortality among injecting drug users: a critical reappraisal. *J Epidemiol Community Health* 1993;**47**:59–63.
31. Hser YI, Hoffman V, Grella CE, Anglin MD. A 33-year follow-up of narcotics addicts. *Arch Gen Psychiatry* 2001 May;**58**(5):503–8.
32. Ghodse AH, Oyefeso A, Kilpatrick B. Mortality of drug addicts in the United Kingdom 1967–1993. *Int J Epidemiol* 1998;**27**:473–8.
33. Chen CC, Kuo CJ, Tsai SY. Causes of death of patients with substance dependence: a record-linkage study in a psychiatric hospital in Taiwan. *Addiction* 2001 May;**96**(5):729–36.
34. Singleton J, Degenhardt LJ, Hall W, Zabransky T. Mortality among amphetamine users: a systematic review of cohort studies. *Drug Alcohol Depend* 2009; **105**:1–8.
35. Fridell M, Hesse M, Jaeger MM, Kuhlhorn E. Antisocial personality disorder as a predictor of criminal behaviour in a longitudinal study of a cohort of abusers of several classes of drugs: relation to type of substance and type of crime. *Addict Behav* 2008 Jun;**33**(6):799–811.
36. Sidney S, Beck JE, Tekawa IS, Quesenberry CP, Friedman GD. Marijuana use and mortality. *Am J Public Health* 1997 Apr;**87**(4):585–90.
37. Rossow I. Suicide among drug addicts on Norway. *Addiction* 1994;**89**(12): 1667–74.
38. Schaar I, Ojehagen A. Predictors of improvement in quality of life of severely mentally ill substance abusers during 18 months of co-operation between psychiatric and social services. *Soc Psychiatr Epidemiol* 2003;**38**(2):83–7.
39. Berglund GW, Bergmark A, Björling B, Grönbladh L, Lindberg S, Oscarsson L, et al. The SWEDATE Project: interaction between treatment, client background, and outcome in a one-year follow-up. *J Subst Abuse Treat* 1991;**8**(3): 161–9.
40. Andersson B, Fridell M, Nilsson K, Tunving K. *The drug addicted patients of the 1970s – patients treated at St Lars hospital 1970–1978*. Lund: The Department of Psychiatry, Lund University; 1986.
41. World Health Organization. *The ICD-10 classification of mental and behavioural disorders and somatic diseases*. Geneva: WHO; 1993.
42. Darke S, Zador D. Fatal heroin overdose; a review. *Addiction* 1996;**91**(12): 1765–72.
43. Ravndal E, Vaglum P. Psychopathology and substance abuse as predictors of program completion in a therapeutic community for drug abusers: a prospective study. *Acta Psychiatr Scand* 1991;**83**(3):217–22.
44. Ravndal E, Vaglum P. Overdoses and suicide attempts: different relations to psychopathology and substance abuse? A 5-year prospective study of drug abusers. *Eur Addict Res* 1999 Jun;**5**(2):63–70.
45. Andreasson S, Allebeck P. Cannabis and mortality among young men: a longitudinal study of Swedish conscripts. *Scand J Soc Med* 1990;**18**(1):9–15.
46. Ödegård E, Amundsen E, Kielland KB. Fatal overdoses and deaths by other causes in a cohort of Norwegian drug abusers, a competing risk approach. *Drug Alcohol Depend* 2007;**89**:176–82.
47. CAN. *Drug trends in Sweden 2005*. Stockholm: Swedish Council for Information on Alcohol and Other Drugs; 2006.